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PROGRESS IN PEDIATRIC NUTRITION

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PROGRESS IN PEDIATRIC NUTRITION

I. Energy and Protein Requirements in the Premature Infant

By RUTH WOODS

Methods involved in the care and handling of premature babies have become so highly specialized and so well perfected within the last ten years, that prematurity, the greatest single cause of death in infancy, may now be regarded as a danger well under the control of modern medical science. One of the major factors contributing to the increased success in preventing mortality in prematures is the progress made toward a better understanding of the nutritional needs peculiar to the premature infant. In this connection it has become important to know not only the specific nutritive requirements, but also to be able to delineate clearly both the abilities and limitations of the premature system in the handling of the various food essentials. The present Review will describe the various modern concepts concerning the nutrition of prematures, with particular reference to the newer theories of protein nutrition.

Characteristics of the Premature Infant:

Before designing a specialized feeding program for the premature infant it is important to establish two fundamental concepts. These are (1) the definition of prematurity and (2) the physiological handicaps characteristic of prematurity.

Definition of Prematurity: Generally speaking, a premature infant is one who is born before the full term—forty weeks—of gestation. However, there are some babies who although of apparently full term gestation are below the anatomic or physiologic standards for mature infants. Such infants must, therefore, be regarded as premature (or immature) and treated accordingly. For practical considerations, any baby weighing less than 5½ lbs. (2500 gm.) at birth is considered as a premature baby, regardless of the period of gestation. Other signs of immaturity include a body length of less than 18 inches (45 cm.) at birth and, of course, a gestation period of from 28 to 38 weeks. The length of the infant (from head to sole) bears a remarkably constant relationship to the maturity of the infant and is little affected by other factors (1). After the 28th week of gestation, the infant measures approxi-

mately half the number of weeks of maturity in inches, i.e. 14 inches at 28 weeks; 16 inches at 32 weeks; etc.

There are also race and sex differences in the birth weights of infants. Negro infants have an average birth weight which is less than that of white infants; female infants of each race have an average birth weight less than that of male infants; the average gestation period for Negro infants is significantly shorter than that for white infants (2). These factors should be considered in an evaluation of the maturity of a given infant.

Physiologic Handicaps of Prematurity: Levine (3, 4) has listed the following as characteristic physiologic handicaps of the premature infant:

Physiologic Handicaps	*Clinical Manifestations*
1. Difficulties of respiration	Asphyxial attacks; aspiration pneumonia
2. Faulty control of body temperature	Chilling or fever
3. Impairment of kidney function	Dehydration; acidosis; azotemia (uremia or retention of nitrogen in blood)
4. Lowered tolerance of alimentary tract	Difficult feeding; vomiting; diarrhea
5. Increased capillary fragility	Hemorrhage
6. Defective blood-forming system	Anemia
7. Increased content of body water	Edema; infections
8. Deficient placental transmission and storage before birth of:	
Minerals and vitamins	Rickets; anemia
Immune substances	Infections
Maternal hormones	Non-appearance of endocrine effects in infants
9. Immature liver function	
Bilirubinemia (pigment in blood)	Jaundice
Hypoglycemia (low blood sugar)	Shock
Hypoproteinemia (low level of plasma proteins)	Edema, infections
Hypoprothrombinemia (low level of clotting factor)	Hemorrhage
10. Incomplete development of enzyme systems, e.g.	
Carbonic anhydrase	Cyanosis (lack of oxygen in blood causing bluish color of skin)
Decarboxylases	Incomplete metabolism of aromatic amino acids
Manufacture of antibodies	Infections
Fetal hemoglobin	Cyanosis

From this it is readily apparent that premature or immature infants present both special feeding problems and special nutrition requirements to compensate for their various physiologic handicaps.

The premature infant has to eat, digest and absorb large amounts of food in order to permit him to grow more rapidly than the infant born at term

with a more efficient digestive apparatus. These heightened demands must be met in the face of:

1. weak sucking and swallowing reflexes
2. inadequate secretion of gastric hydrochloric acid and digestive enzymes
3. faulty fat absorption
4. faulty absorption of vitamin A and other fat-soluble vitamins and of certain minerals

The high incidence of hemorrhage, anemia and infection in prematures calls for heightened nutritional requirements to overcome actual losses, to compensate for inadequate or incomplete prenatal stores and to overcome the added stresses imposed by very rapid growth and by the debilitating effects of infection.

The premature infant thus has a dual problem: (1) that of overcoming nutritional deficiencies caused by inability to cope efficiently with foods and (2) that of overcoming nutritional deficiencies caused by the exceptionally heightened requirements resulting from a poor start (deficient storage of nutrients from maternal stores) and from the demands of stress factors such as growth and infection.

Growth Rate in the Premature Infant:

Premature babies lose more weight in the first few days of life than do full-term babies. Further, they regain their birth-weights at a much slower rate, often taking up to three weeks in the case of the smaller infants. However, the birth-weight may be doubled in 2-3 months, trebled in 5-6 months and at the age of one year, the weight reached may be as much as five or six times the birth-weight. This is considerably in excess of the weight gains of full-term babies. (i.e. The average weight at one year is about 21 lbs. For a full-term 7 lb. infant this would be a triple increase of birth-weight; for a 4½ lb. premature this would be nearly a five-fold increase.) The need for rapid growth of the premature baby explains his high caloric requirements, and his great need for tissue-building protein and for vitamins and minerals.

Optimal Weight Gains for Prematures: First Two Weeks: The amount and type of food required by the premature infant must be determined by his needs (for rapid growth and to compensate for inadequate stores) and by his digestive abilities and limitations.

A considerable difference of opinion exists as to the caloric requirements and desired weight gains of the premature, particularly in the critical first

two weeks of life. Sufficient food must be given to maintain life and to avoid the results of underfeeding:—lethargy, inanition, fever, cyanosis, loss of weight and dehydration. However, overfeeding must also be avoided with its attendant dangers:—abdominal distention, vomiting and diarrhea, leading likewise to loss of weight and dehydration.

According to Hess and Lundeen (5) the tendency to overfeed the young premature baby is one of the most important factors in the mortality and morbidity of the first few weeks of life. Similarly, Crosse (1) believes that the dangers of overfeeding are far greater than those of underfeeding. She states, "minimum feeding gives the highest survival rate, the least abdominal distention, diarrhea and vomiting, and the most consistent gain in weight (slow but sure)." The suggested "minimum" requirements in terms of volume of fluid intake are listed in Table 1.

Table 1. Fluid Requirements During First Two Weeks (1)

Age of Baby	*Approx. Daily Fluid Requirements*
3rd-4th day	1 oz. per pound birth-weight*
7th day	2 ozs. " " " "
10th-11th day	2½ ozs. " " " "
14th day	3 ozs. " " " "
After 14th day	3-3½ ozs. " " " "

*After the birth-weight has been regained, the actual body weight is used as the weight on which calculations are made, but until then the birth-weight is used.

Caloric Requirements: (The "Minimal" Theory): A great diversity of opinion exists as to the proper caloric intake for prematures even after the first week or two, various authors recommending from 75 to 200 calories or even more per kilo of body weight per day (6, 7). According to Crosse (1) a safe suggestion is to give the smallest number of calories on which the baby gains a small, but consistent amount. A suggested standard of weight gain for prematures, according to this author, is not more than:

½ oz. per day for babies weighing 2-2½ lbs.
1 oz. per day for babies weighing 4-5 lbs.

Any greater gain, Crosse believes, puts a strain upon the digestive system and may lead to serious upsets. She emphasizes the fact that: *"Survival is of more importance than a rapid gain in weight. The optimum gain in weight and the largest gain in weight have not yet been proved synonymous terms."* As a result, the caloric requirements *during the first two weeks* are designed to meet *maintenance requirements* only, extra calories for growth requirements being delayed until the infant has matured somewhat and has adjusted to the problems of handling food. The maintenance allowance is set at about

20-25 cal./lb. daily* (compared to about 28 cal./lb. for maintenance in a full-term infant) and may be reached gradually by as late as the 7th-10th day of life. During this time the infant draws upon fat stores which, although small, are adequate for their very limited early needs.

Energy and Protein Requirements of Premature Infants:

Before an accurate determination of requirements can be made, the nature of the food being used must be clearly understood. There are, for example, considerable differences between human milk and cow's milk and the many modifications of the latter which are in use. The ability of the premature infant to utilize the essential components of these various milks must be established and compared to the utilization of the same components in human milk.

Utilization of Protein from Human Milk and From Cow's Milk: About thirteen years ago, Gordon, Levine, Wheatley and Marples (8) attempted for the first time to determine scientifically the quantitative ability of premature infants to retain the nitrogen of cow's milk. Prior to that time, isolated studies had been made, chiefly by European workers (9, 10, 11, 12, 13, 14, 15) on nitrogen balance in infants on human milk only. The studies of Gordon *et al* were undertaken in order to establish the validity of the popular belief that the protein of human milk is better retained than that of cow's milk. While this seemed to be so at first glance from previous studies of their own on nitrogen balance in prematures (16) they pointed out that such a conclusion is unwarranted because the infants on the two types of diet received protein differing not only in quality, but also in amount. Accordingly, they made observations on infants fed human milk and on infants fed cow's milk modified to resemble human milk in calories, protein, fat, carbohydrate and fluid content. The average amounts of nitrogen retained by the infants (in periods lasting several days up to two weeks) were identical, being 0.25 gm. per kg. per 24 hrs. for those on human milk and 0.27 gm./kg./24 hr. for those on modified cow's milk. The percentages of utilization were 70.9 and 70.5, respectively, considerably higher than those observed in full-term babies. The absorption of fat from both milks was defective as compared with that of full-term infants, but the utilization of protein from both products was unlimited. Increasing the protein content of cow's milk at the expense of the fat (either butterfat or butterfat partially replaced with olive oil) increased the amount of nitrogen retained.

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*About 40-50 cal. per kilo.

Energy Requirements: In a continuation of their studies on the metabolism of premature infants, Gordon, Levine and coworkers (16) investigated the daily energy exchange of a group of such infants. Calculations included basal metabolism, specific dynamic action of food, and activity, as well as caloric loss via excretory products. On the basis of these observations, they concluded that a daily intake providing 120 calories per kg. of body weight amply covers maintenance energy requirements and provides a reasonable surplus for satisfactory weight gain in premature infants over two weeks of age.

The authors comment, therefore:

> "The finding that diets containing an average of 120 calories per kilo of body weight per day covered the energy requirements of a group of thriving premature infants prompted closer scrutiny of the practice of feeding between 150 and 200 calories per kilo. Such practice is based partly on the acceptance of maximal rates of weight gain as optimal and partly on the opinion that premature infants require a greater caloric intake than do full term infants because of more rapid rate of growth.
>
> "What constitutes optimal growth for the premature infant is not yet established, but it seems reasonable to accept the rate of weight gain in utero as one criterion of such growth. The latter may be calculated . . . as approximately 15 grams per kg. per day for infants of 1,000 gm. (about 2 lbs.) and 10 grams per kg. for infants of 2,000 grams (about 4 lbs.). In these observations a total caloric intake averaging 120 cal./kg. covered all energy needs and permitted a gain of 16 gm. per kg., as compared with the theoretic optimum gain of 10 gm./kg. per day for the group of infants studied."

With regard to the popular belief that premature infants need more calories than full term infants because of their greater rate of growth, the authors point out two important facts that cast doubt upon the validity of this premise:

> "The slightly greater amount of energy stored incident to optimal gains of 10 to 15 rather than 8 to 10 gm. of tissue per kg. per day hardly serves as an excuse for feeding diets that are from 100 to 150 per cent above the maintenance requirements.
>
> "Without discussing in detail the large variety and interrelationships of . . . factors which influence growth, it seems reasonable to postulate that high caloric intakes permit rapid weight gains, rather than the converse, that a high rate of growth requires a high caloric intake."

In accord with the opinions of Hess and Lundeen (5), Crosse (1), Holt (17) and others, Gordon, Levine and associates believe that too high a caloric intake (150 to 200 calories per kg.) may have serious consequences. Firstly, the infant's food tolerance may be exceeded causing gastrointestinal

upset—particularly in view of the existing physiologic handicaps of the infant (page 52); secondly, a too rapid gain in weight may impose stress conditions leading to the development of rickets and anemia.

High Carbohydrate—High Protein—Low Fat Diets vs. High Calorie Diets:

Comparative studies of fat absorption were made in premature and full-term infants receiving isocaloric diets containing equivalent amounts of fat (18). While 9 of the 10 full-term infants studied excreted 10 calories or less per kg. of body weight per day as fecal fat, only 6 of the 31 premature babies showed similar values, the remaining 25 exceeding this value by an appreciable amount. In 9 of the prematures (29%) the excretion of fecal fat reached the high level of 20 cal./kg./day or more.

Other studies indicated a similar metabolic defect in prematures regardless of the type of fat eaten (19), i.e. butter fat or olive oil. Although differences in the splitting of the fats were observed (88 to 93% of butterfat split; 55 to 67% of olive oil split), the total fat excretion was essentially the same, indicating the metabolic defect is one of absorption and transport of fat across the intestinal wall.

On the basis of these observations, Levine and Gordon (20) attribute the failure of some premature infants to thrive on the presumably adequate diets containing 120 cal./kg. to excessive loss of unabsorbed fat in the feces. While the general clinical practice has been to increase the total calories in such cases, Levine and Gordon suggest the preferable alternative of replacing some of the fat with protein and carbohydrate both of which are completely utilized. Thus, the total calories would remain the same, the only difference being that the wasted calories resulting from non-utilized fat would be replaced by useful calories from protein and carbohydrate.*

Levine and Gordon, therefore, recommend the feeding of milk mixtures containing 120 cal./kg., 150 cc. of fluid, not more than 2½ grams of fat per kg. and relatively large amounts of carbohydrate (18 gm.) and protein (6 gm.) for optimal growth in premature infants (20, 21).

In order to provide a milk of this specification these authors have found it advisable to use a cow's milk formula in place of breast milk which is

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*In the full fat diet, therefore, the baby is not really getting the prescribed 120 cal./kg., but anywhere from 100 to 110 cal./kg. because of the unused fat lost in the feces. The substitution of protein and carbohydrate thus effects a real increase in *available* calories without exceeding the figure of 120/kg.

customarily regarded as the food of choice for all infants. The reasons for this are twofold:

1. Prematures, especially the smaller ones, are unable to nurse from the breast and must be fed artificially whether the milk is human or cow's. Human milk must be diluted, boiled or pasteurized, etc., so that it no longer approximates the original product in any case.
2. Cow's milk has more than twice the protein content of human milk; the fat content is easily reduced by removing half the cream. Human milk is low in protein and is very difficult to skim.

The preparation of a formula of this type is further simplified by the availability of dried milk products especially modified to meet these specialized requirements. Such products can be reconstituted with sterile water to give formulas of varying strengths as needed, but with a constant low fat-high carbohydrate and protein ratio.

Role of Protein Hydrolysates: Some pediatricians, while firmly convinced of the superiority of human milk for the human infant by virtue of natural design and intent, nevertheless are aware of the fact that it presents certain deficiencies with respect to meeting the unique requirements of the premature baby. For one thing the caloric content is low, necessitating the intake of a greater volume of milk than might be desirable for the limited digestive capacity of the infant. Also, the protein content, an important factor in growth and in the building of tissue, is very low. As a compromise, therefore, Magnusson (2) in Stockholm suggested, about six years ago, the use of hydrolyzed casein* as a supplement to mother's milk for the triple purpose of (1) increasing calories, (2) increasing protein and (3) providing easily assimilable amino acids instead of undigested protein to tax the digestive facilities of the infant. From comparative studies with a non-hydrolyzed casein preparation of identical composition, the superior weight gains with the amino acids were attributed not so much to the extra calories provided as to the fact that the protein in the pre-digested form was more efficiently utilized. The weight gains on human milk supplemented with the casein hydrolysate were markedly superior to those on human milk alone. These findings were subsequently confirmed in a later study involving a larger number of infants (23).

Similar studies with a casein hydrolysate added to human milk, evaporated cow's milk, powdered whole milk, and powdered half-cream milk were reported in March of this year by the British investigators, Young,

*A mixture of hydrolyzed casein plus glucose and mineral salts was used in amounts of about 10 cc. per kg. of body weight and provided about 2.5 gms. of amino acids/kg. body weight.

Poyner-Wall and associates (24). They found that premature infants tolerate the hydrolysate well, but that desirable weight gains were achieved only when the calorie content of the diets was enhanced by the addition of glucose as in the experiments of Jorpes *et al* (23). Young *et al* found that the average rate of gain in weight (from the third week after birth) by premature infants receiving adequate diets (containing extra protein and calories) is the same as that of the fetus *in utero* and they believe, therefore, that this should be regarded as a standard. This is in agreement with the opinions of Gordon and Levine and Jorpes *et al* (average caloric intake recommended, 120 cal./kg.) but in contrast to the beliefs of Hess and Lundeen 80-100 cal./kg./day up to one month of age as well as those of other workers who recommend higher caloric intakes (i.e. 150-200 or more cal./kg./day).

An important recommendation for all premature babies on high protein diets is that they must also receive adequate amounts of supplementary ascorbic acid which has been found essential for the complete metabolism of the aromatic amino acids (25).*

Conclusion:

Modern advances in pediatric nutrition have contributed, in a marked degree, to the reduction of mortality in premature infants. Although variations in opinion among pediatricians exist, several general principles seem to be well established on the basis of the findings derived from current clinical research. These are briefly:

1. Premature infants should be fed the minimal amounts of fluid and calories compatible with maintenance requirements during the first 10 to 14 days of life. This is to avoid taxing the immature digestive facilities and to minimize stress on the infant poorly equipped with sucking, gag, cough and swallowing reflexes. Overfeeding may cause aspiration of food into the lungs with resultant pneumonia or it may result in abdominal distention, vomiting, dehydration, both courses having possible fatal consequences.
2. Premature infants are born with very inadequate nutrient stores, particularly of proteins and minerals. After the first week or two they should be given supplementary protein and calories to permit a desirable rate of growth, comparable to that which they would have exhibited had they remained *in utero* until term. A recommended diet provides 120 calories per kg. of body weight per day and about 6 grams of protein. Amounts less than this are generally inadequate for

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**cf. Borden's Review of Nutrition Research*—Sept. 1949.—"Dietary Interrelationships—Vitamin C and the Metabolism of Aromatic Amino Acids."

good growth; amounts greater than this may precipitate the dangers attendant on overfeeding (see above) and too rapid growth (anemia, rickets).

3. Premature babies do not utilize fat as well as do full-term babies. It is therefore suggested that part of the fat be removed from the milk and replaced with isocaloric amounts of protein and carbohydrate, both of which are very efficiently utilized.

The vitamin and mineral requirements of the premature baby will be discussed in a future Review.

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NEWS DIGEST

VITAMIN B_{12} and THYROPROTEIN: Growth depression in rats has been induced by feeding the hormone, diethylstilbestrol. The action of the hormone has been attributed to its ability to reduce appetite. It was believed that the inhibiting effects of the hormone were induced by increasing certain vitamin needs or by decreasing thyroid secretion, or both. This hypothesis was tested by treating five evenly divided groups of 50 male rats for 20 days. Diethylstilbestrol and thyroprotein were fed in a commercial ration, while B_{12} was injected subcutaneously at a level of 0.2 microgram daily. During the first ten days, B_{12} failed to counteract the growth depression induced by diethylstilbestrol, but partially overcame the effects of the latter during the last ten days. Thyroprotein plus diethylstilbestrol induced greater growth inhibition than the latter alone. Addition of B_{12} to the diethylstilbestrol-thyroprotein combination completely counteracted the growth-inhibiting action of the latter and only slightly that of the former. Food intake was increased both by vitamin B_{12} and thyroprotein.—*Fed. Proc. 9,* 87 (1950).

SELF-SELECTION OF DIET BY CHICKS: Studies were made with day-old chicks fed mash and grain free choice. A typical chick starter mash was used in which the protein content was varied from 20.3 to 31.6 percent by removal of corn and oats. The feed hoppers were left in the same position throughout the six-week trials. It was found that the chicks failed to select enough mash when the 20.3 percent protein mash was given. However, chicks which had their choice between finely cracked corn and a 31.6 percent protein mash selected an average protein level of 21.7 percent and grew uniformly and optimally (485 grams at 6 weeks—22 chicks). About equal parts of corn and mash were selected although this varied somewhat between experiments.

From the data, it was concluded that chicks are able to select their correct protein level under these conditions but only when a high protein mash is fed with the grain. The authors point out that the effect of chance in selecting the correct level must be considered as well as the need for vitamins and minerals in addition to the need for protein. — *Poultry Science 28,* 758 (1949).

NEW CHICK GROWTH FACTOR: Studies have been conducted on the multiplicity of factors required for growth of chicks receiving purified diets containing extracted protein from soybeans. The experimental period was preceded by a 2-week preliminary period during which time the basal diet was fed. At the end of this period, the chicks were distributed into uniform experimental groups on the basis of body weight. The addition of crystalline vitamin B_{12} to the diets used resulted in a lower growth response of chicks as compared to that obtained when a special liver extract was used. Furthermore, when dried whey was fed in combination with a vitamin B_{12} crude concentrate better growth was obtained than when the vitamin B_{12} crude concentrate was fed alone. The results of these studies strongly indicate, therefore, that at least one unidentified factor, which is not identical with vitamin B_{12}, is required for rapid growth in the chick. This unidentified factor is present in liver and dried whey.—*Poultry Science 28,* 775 (1949).

VITAMIN THERAPY IN SCHOOL CHILDREN: A study has been made of school children having one or more of the usually accepted physical signs of deficien-

cies of vitamin A, ascorbic acid, niacin or riboflavin for seasonal periods in each of three consecutive years. Children were grouped according to type and severity of lesion, sex and age (under and over 12 years of age). Four groups—vitamin A, ascorbic acid, niacin and riboflavin—were established and each group was subdivided into control and therapy sections. Therapy was administered with each of the above vitamins in amounts approximately four times the recommended daily dietary allowances of the National Research Council. Bloods were analyzed for hemoglobin, serum protein, alkaline phosphatase, vitamin A, carotene and ascorbic acid in the spring, fall and winter by microchemical methods. Vitamin A blood levels were significantly elevated by vitamin A therapy and not significantly changed by the other three types of therapy. Ascorbic acid therapy resulted in a significant elevation of blood ascorbic acid, but no such effect was observed with the other three types of therapy. The ascorbic acid therapy group had significantly lower carotene levels than control children, other types of therapy having no significant effect upon blood carotene. Hemoglobin and serum protein levels were not significantly improved by the therapy used. Children in all therapy groups showed a significantly greater increase in height and a tendency to increase more in weight than children in control groups. — *Fed. Proc. 9,* 368 (1950).

A NEW, NON-CAROTENE PROVITAMIN A: In the course of other studies on the fat metabolism of marine organisms, examination of a routine fat extraction of zooplankton revealed an extract of deep red color containing a significant percentage of carotenoid pigments. The material was therefore investigated as a possible source of provitamin A for fishes. Certain fish are known to use carotene effectively as a precursor of vitamin A. When given the zooplankton oil, however, the liver vitamin A storage response of the fish was at least 30 times as large as might have been predicted on the basis of the actual carotene content of the oil administered. Fractionation of the oil revealed that all of the provitamin A activity resided in the non-carotenoid filtrate fraction. The authors thus conclude that some fishes apparently can utilize zooplankton pigments other than the common carotenoids as raw materials for the manufacture of vitamin A.—*Science 111,* 471 (1950).